A 34-year-old man is brought to the emergency department after a motor vehicle collision. He has blunt abdominal trauma and bilateral femur fractures. The patient has no significant medical history and takes no medications. He does not smoke but drinks 8-12 alcoholic beverages a day. Blood pressure is 80/40 mm Hg and pulse is 110/min. Immediate resuscitation efforts are initiated, during which he receives transfusion of several units of packed red blood cells. During transport to the intensive care unit, the patient reports a tingling sensation in his fingers and toes. Serum ionized calcium level is 4 mg/dL (normal: 4.8-5.5). Which of the following is the most likely cause of this patient's current symptoms?

A. Antibody-mediated red blood cell membrane damage

B. Calcium chelation by a substance in the transfused blood

C. Electrolyte leakage from red blood cells during pretransfusion storage

D. Increased renal tubular excretion of calcium

E. Release of intracellular contents from injured muscle

Submit

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A. Antibody-mediated red blood cell membrane damage (6%)

✓ B. Calcium chelation by a substance in the transfused blood (71%)

C. Electrolyte leakage from red blood cells during pretransfusion storage (4%)

D. Increased renal tubular excretion of calcium (6%)

E. Release of intracellular contents from injured muscle (11%)

Omitted
Correct answer
B

71%
Answered correctly

03 secs
Time Spent

03/31/2020
Last Updated

Explanation

Acute hypocalcemia	
Causes	• Neck surgery (parathyroidectomy) • Pancreatitis • Tumor lysis syndrome

Acute hypocalcemia	
Causes	• Neck surgery (parathyroidectomy) • Pancreatitis • Tumor lysis syndrome • Chelation: blood (citrate) transfusion

Clinical features	• Peripheral neuromuscular excitability (tetany)
	  ◦ Chvostek sign (facial muscle spasm)
	  ◦ Trousseau sign (carpopedal spasm)
	  ◦ Paresthesias, hyperreflexia
	• Seizures

Treatment	• IV calcium gluconate/chloride

IV = intravenous.

This patient has symptomatic hypocalcemia (eg, paresthesias) following **high-volume blood transfusion**. Prior to storage, donated blood is generally mixed with solutions containing **citrate** anticoagulant. Following transfusion, citrate is rapidly metabolized to bicarbonate in the liver; however, when large volumes of blood are transfused rapidly, the excess citrate can **chelate calcium** in the plasma, leading to **hypocalcemia** due to decreased serum ionized calcium concentration. This is most common with very high transfusion rates (eg, >9 units/hr), but it can also be seen at lower rates in patients with underlying hepatic insufficiency (eg, alcoholic liver disease).

Other complications of high-volume transfusion include depletion of coagulation factors and volume overload.

(Choices A and C) Antibody-mediated hemolysis is typically caused by transfusion of ABO-incompatible blood. Characteristic clinical findings include fever, back or flank pain, acute kidney injury, and hemoglobinuria. The primary electrolyte complication is hyperkalemia due to release of intracellular potassium. Hyperkalemia can also be seen due to leakage of potassium from red cells during storage. However, hypocalcemia would not occur in these scenarios.

(Choice D) Acute hypocalcemia due to increased renal calcium excretion can be seen in hypoparathyroidism. This is commonly encountered as

IV = intravenous.

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(Choice D) Acute hypocalcemia due to increased renal calcium excretion can be seen in hypoparathyroidism. This is commonly encountered as a complication of thyroid or other neck surgery with inadvertent injury or removal of the parathyroid glands. Abdominal and lower extremity trauma would not affect parathyroid function.

(Choice E) Rhabdomyolysis typically presents with muscle pain, red urine (ie, myoglobinuria), and elevated creatine kinase. Release of intracellular phosphate from muscle cells can precipitate calcium salts in damaged muscle and lead to hypocalcemia, but this is typically a delayed finding (24-72 hours after trauma).

Educational objective:
Citrate anticoagulants in high-volume blood transfusion can chelate plasma calcium, leading to hypocalcemia which causes peripheral neuromuscular excitability (eg, paresthesia, muscle spasms). This is most common with very rapid transfusion rates, but it can also be seen at lower rates in patients with hepatic insufficiency because citrate is metabolized by the liver.

References

- Hypocalcemia in trauma patients receiving massive transfusion.

Physiology Hematology & Oncology Blood transfusion

A 62-year-old man comes to the office due to worsening fatigue. The patient has long-standing type 2 diabetes mellitus complicated by nephropathy. Laboratory results are as follows:

Hemoglobin	9.4 g/dL
Mean corpuscular volume	90 μm^3
Platelets	200,000/mm^3
Leukocytes	7,500/mm^3
Serum creatinine	3.2 mg/dL
Total bilirubin	0.8 mg/dL
Serum ferritin	350 ng/mL
Transferrin saturation	30% (normal: 20%-50%)

After appropriate treatment is initiated for his anemia, which of the following changes is most likely to occur in this patient's erythroid cells?

A. Decrease in free protoporphyrin levels
B. Decrease in reticuloendothelial destruction
C. Increase in progenitor cell differentiation
D. Switch of hemoglobin to the fetal form
E. Synchronization of nuclear and cytoplasmic maturation

Submit

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Transferrin saturation	30% (normal: 20%-50%)

After appropriate treatment is initiated for his anemia, which of the following changes is most likely to occur in this patient's erythroid cells?

A. Decrease in free protoporphyrin levels (26%)
B. Decrease in reticuloendothelial destruction (8%)
✓ C. Increase in progenitor cell differentiation (57%)
D. Switch of hemoglobin to the fetal form (0%)
E. Synchronization of nuclear and cytoplasmic maturation (6%)

Omitted
Correct answer
57%
01 sec
02/06/2020

Explanation

Patients with **chronic kidney disease** (CKD) often develop **normocytic anemia** as the glomerular filtration rate worsens due to **inadequate production of erythropoietin** (EPO), a glycoprotein hormone produced by peritubular fibroblast cells in the renal cortex. EPO is released into the bloodstream in response to renal tissue hypoxia and subsequently acts on erythrocyte progenitor cells (erythroid colony–forming unit cells) in the bone marrow to reduce apoptosis and increase **differentiation** into mature red blood cells.

Although healthy individuals respond to anemia by increasing EPO levels up to 10,000-fold, patients with CKD have chronic inflammatory damage to renal EPO-producing cells and are often unable to generate sufficient levels of EPO to maintain adequate erythrocytosis. These individuals are often treated with **synthetic forms of EPO** (eg, epoetin, darbepoetin) to supplement intrinsic EPO production and stimulate erythropoiesis. Because synthetic forms of EPO can rapidly deplete iron stores (due to increased red blood cell production), patients should be tested for iron deficiency prior to treatment with these agents.

(Choice A) Protoporphyrins (heme precursors) are elevated in patients with iron deficiency anemia. Treatment of iron deficiency anemia (eg, iron supplementation) leads to the conversion of protoporphyrins to heme, thereby reducing free protoporphyrin levels. Patients with iron deficiency anemia usually have low serum ferritin levels and transferrin saturation.

(Choice B) Warm autoimmune hemolytic anemia is characterized by antibodies against antigens on the red cell membrane that result in phagocytosis in the reticuloendothelial system (eg, spleen). Autoimmune hemolytic anemia is usually treated with immune-suppressing agents (eg, prednisone), which blunt antibody production and reduce red cell destruction. This patient with a normal bilirubin level is unlikely to have hemolytic anemia.

(Choice D) Sickle cell anemia is caused by mutations in the beta globin chain, which results in the polymerization of deoxygenated hemoglobin molecules ("sickling"). Treatment with hydroxyurea induces expression of fetal hemoglobin (which is unaffected by the sickle mutation) over adult hemoglobin, thereby preventing polymerization of hemoglobin molecules.

(Choice E) Deficiency of vitamin B_{12}/folate (megaloblastic anemia) impairs nucleic acid metabolism, which results in slowed production of erythrocyte precursors in the bone marrow. Replacement of vitamin B_{12}/folate corrects the anemia by improving nuclear maturation. Megaloblastic anemia is typically associated with macrocytic (elevated mean corpuscular volume) anemia.

Educational objective:
Erythropoietin (EPO) is produced by peritubular fibroblast cells in the renal cortex in response to decreased renal oxygen delivery. EPO acts on

Although healthy individuals respond to anemia by increasing EPO levels up to 10,000-fold, patients with CKD have chronic inflammatory damage to renal EPO-producing cells and are often unable to generate sufficient levels of EPO to maintain adequate erythrocytosis. These individuals are often treated with **synthetic forms of EPO** (eg, epoetin, darbepoetin) to supplement intrinsic EPO production and stimulate erythropoiesis. Because synthetic forms of EPO can rapidly deplete iron stores (due to increased red blood cell production), patients should be tested for iron deficiency prior to treatment with these agents.

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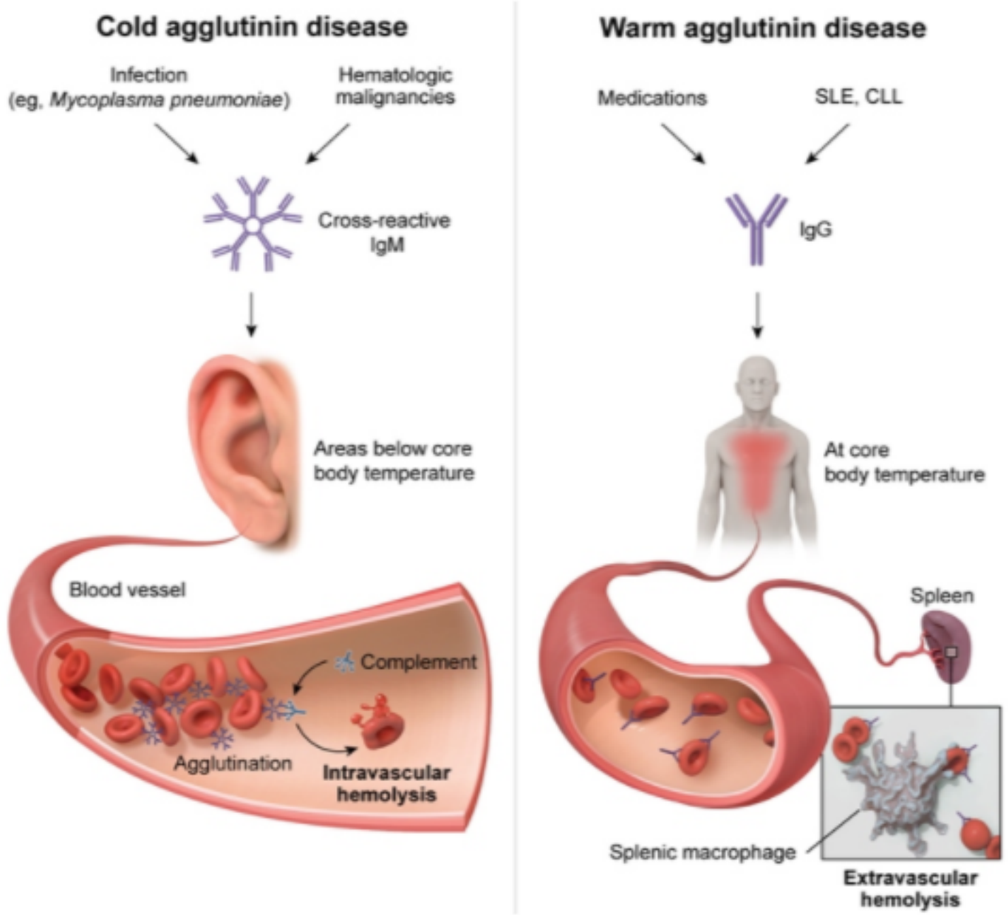
Educational objective:
Erythropoietin (EPO) is produced by peritubular fibroblast cells in the renal cortex in response to decreased renal oxygen delivery. EPO acts on erythrocyte precursors in the bone marrow to increase red blood cell production. Patients with chronic kidney disease often have damage to renal EPO-producing cells, which results in normocytic anemia.

References

- Renal erythropoietin-producing cells in health and disease.

Exhibit Display



CLL = chronic lymphocytic leukemia; SLE = systemic lupus erythematosus.

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References

- Renal erythropoietin-producing cells in health and disease.

Physiology	Hematology & Oncology	Anemia of inflammation
Subject	System	Topic

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A 35-year-old man is brought to the emergency department after collapsing in his garage. He recently bought a classic 1960s convertible and was repairing it when he collapsed. The patient was inside the garage but had the door half-open. He lost consciousness after working on the car for 2 hours with the engine running. The patient has no known medical problems and takes no medications. He does not use tobacco, alcohol, or illicit drugs. Which of the following best reflects the combination of findings that would have been expected in an arterial blood sample taken when the patient lost consciousness?

	Carboxyhemoglobin (%) [normal = 0-2]	PaO_2 (mm Hg)[normal = 85-100]	Methemoglobin (%) [normal = 0-1]
A.	2	95	30
B.	35	45	1
C.	35	45	25
D.	40	95	1
E.	40	95	25

Submit

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	Carboxyhemoglobin (%) [normal = 0-2]	PaO_2 (mm Hg)[normal = 85-100]	Methemoglobin (%) [normal = 0-1]
A. (4%)	2	95	30
B. (27%)	35	45	1
C. (15%)	35	45	25
✓ D. (44%)	40	95	1
E. (7%)	40	95	25

Omitted
Correct answer
D

44%
Answered correctly

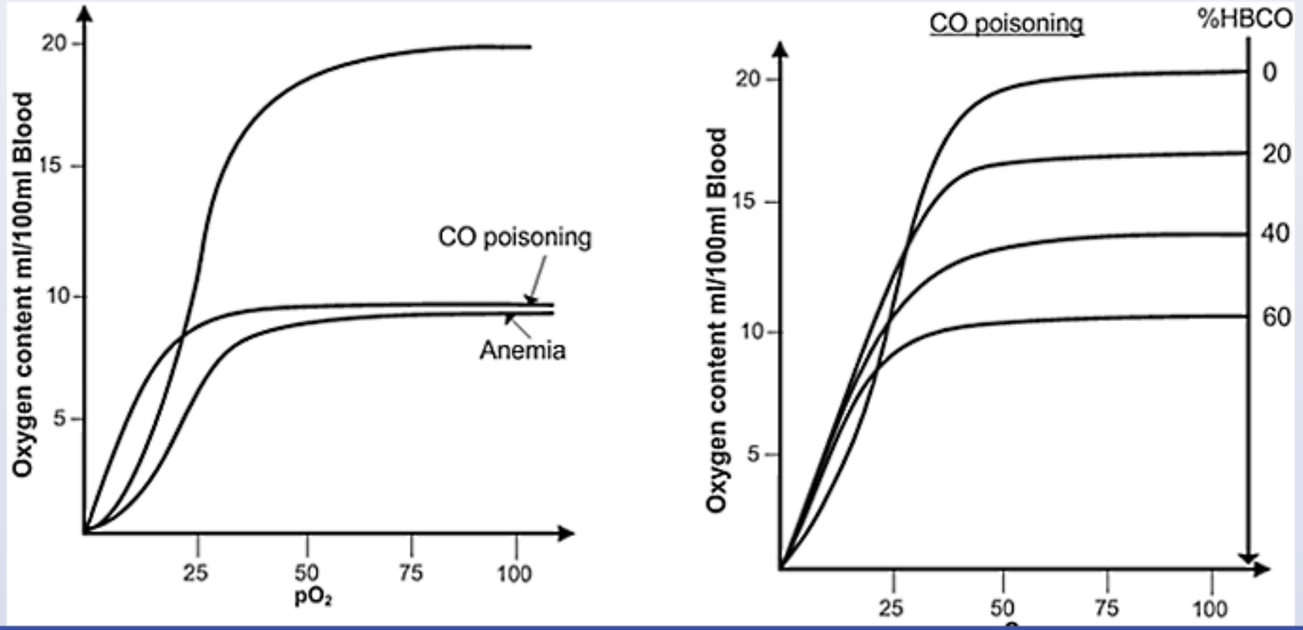
02 secs
Time Spent

05/05/2020
Last Updated

Carbon monoxide (CO) is a colorless, odorless gas product of the combustion of carbon-containing compounds. CO poisoning can occur after exposure to automobile exhaust (especially in older cars without catalytic converters), fire smoke, or improperly vented natural gas appliances. CO has 2 major effects on oxygen delivery to tissues:

1. CO binds to hemoglobin with an affinity approximately 250 times that of oxygen, reducing the number of heme binding sites available to oxygen. As a result, levels of CO-bound hemoglobin, represented by **carboxyhemoglobin** (HBCO), **increase**. By decreasing the fraction of hemoglobin available for oxygen binding, CO decreases the oxygen-carrying capacity and **oxygen content** of blood, but **not** the amount of oxygen **dissolved** in plasma, reflected by the partial pressure of oxygen (PaO_2).
2. CO poisoning causes a **leftward** shift of the hemoglobin-oxygen dissociation curve, reflecting a decreased tendency for oxygen to unload in the tissues.

CO's effects on arterial blood oxygen content are seen in the graphs below, which show the lower oxygen content with CO poisoning (similar to anemia) and the leftward shift of the dissociation curve that becomes increasingly more pronounced at increasingly higher HBCO concentrations (this does not occur with anemia).



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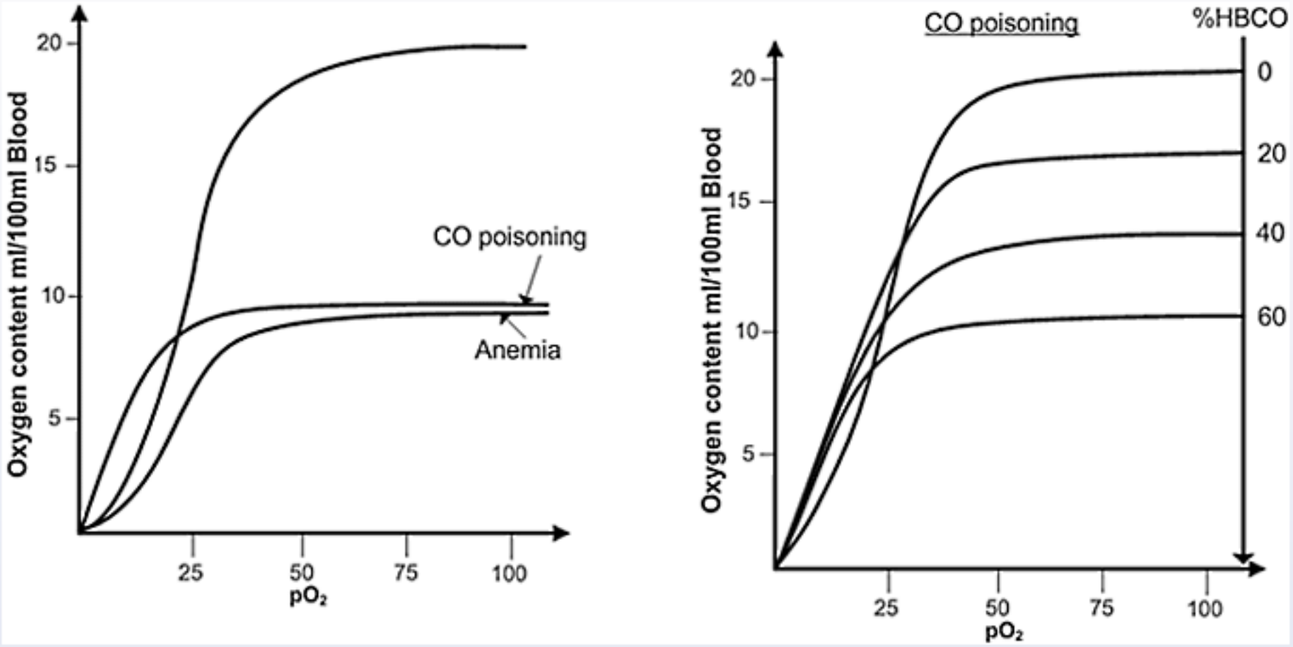
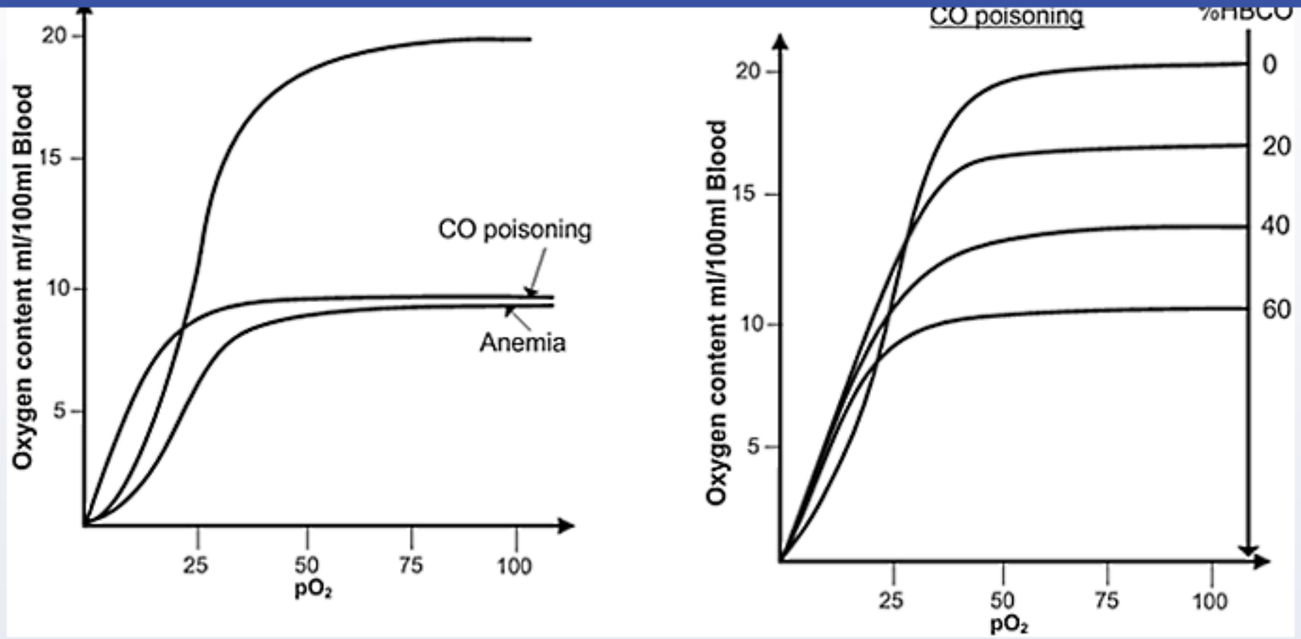


(Choices A, B, C, and E) CO poisoning does not affect PaO_2 and it does not cause methemoglobinemia. Methemoglobin is formed when the Fe^{2+} (ferrous iron) in heme is oxidized to Fe^{3+} (ferric iron). Methemoglobinemia results from drug exposures (ie, dapsone, nitrites) as well as enzyme deficiencies and hemoglobinopathies.

Educational objective:

Carbon monoxide (CO) binds to hemoglobin with much higher affinity than oxygen, thereby preventing oxygen binding to hemoglobin. It also reduces oxygen unloading from hemoglobin in the tissues. CO poisoning increases carboxyhemoglobin concentrations but does not affect the partial pressure of oxygen and does not precipitate methemoglobinemia.

Physiology	Hematology & Oncology	Carbon monoxide poisoning
Subject	System	Topic



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Physiology	Hematology & Oncology	Carbon monoxide poisoning
Subject	System	Topic

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A 66-year-old man with hypertension and stage IV chronic kidney disease comes to the office for follow-up. The patient has had worsened fatigue and low energy over the past several months but no chest pain or shortness of breath. He was previously nonadherent with antihypertensive therapy but has been following treatment recommendations since renal dysfunction was diagnosed 2 years ago. Blood pressure is 126/78 mm Hg and pulse is 68/min. Cardiac auscultation reveals an S4 sound. The rest of the physical examination is unremarkable. Laboratory results show normocytic, normochromic anemia with a low reticulocyte count. Serum iron studies are within normal limits. Treatment with a recombinant glycoprotein hormone is begun, and repeat laboratory testing several weeks later shows an improvement in hemoglobin level. The effects of the hormone prescribed for this patient are most likely mediated by which of the following pathways?

A. Adenylate cyclase/cyclic AMP

B. Arachidonic acid/phospholipase A2

C. Janus kinase 2/signal transducers and activators of transcription

D. Nuclear receptors

E. Phosphatidylinositol 3-kinase

F. Ras/mitogen-activated protein kinase

Submit

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- A. Adenylate cyclase/cyclic AMP (6%)
- B. Arachidonic acid/phospholipase A2 (1%)
- ✓ C. Janus kinase 2/signal transducers and activators of transcription (73%)
- D. Nuclear receptors (10%)
- E. Phosphatidylinositol 3-kinase (2%)
- F. Ras/mitogen-activated protein kinase (4%)

Omitted
Correct answer
C

73%
Answered correctly

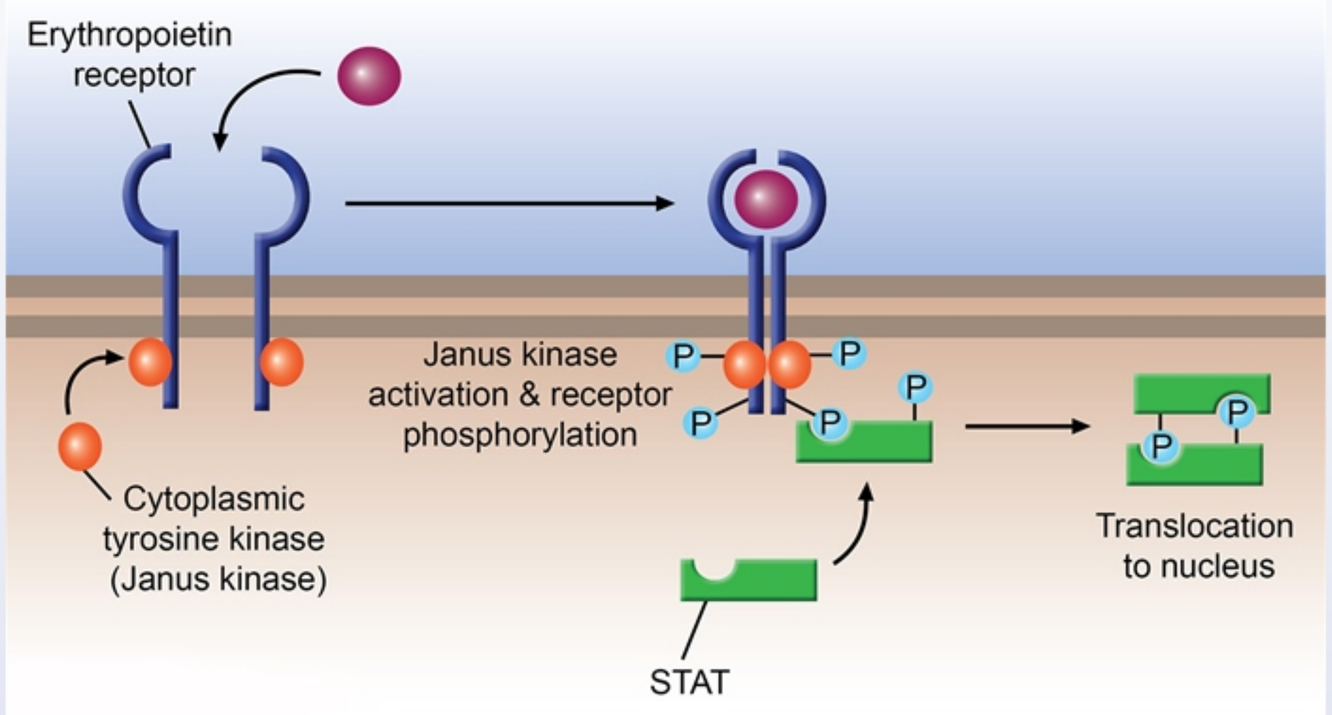
01 sec
Time Spent

01/28/2020
Last Updated

Explanation

Erythropoietin signal transduction

Erythropoietin signal transduction



STAT = signal transducers and activators of transcription.

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Patients with **chronic kidney disease** (CKD) often develop **normocytic anemia** as the glomerular filtration rate declines, due to an inability to generate adequate quantities of erythropoietin (EPO). EPO is a glycoprotein produced by peritubular fibroblast cells in the renal cortex in response to tissue hypoxia (as seen with anemia). Healthy individuals increase EPO production up to 10,000-fold in response to anemia, but patients with CKD have chronic renal inflammation that **damages EPO-producing cells**, thereby preventing an adequate EPO response. Therefore, patients with CKD are often treated with **recombinant EPO agents** (eg, epoetin, darbepoetin) to supplement EPO production.

EPO travels from the kidney through the bloodstream to the bone marrow, where it binds to a surface receptor on **erythrocyte colony–forming**

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Patients with **chronic kidney disease** (CKD) often develop **normocytic anemia** as the glomerular filtration rate declines, due to an inability to generate adequate quantities of erythropoietin (EPO). EPO is a glycoprotein produced by peritubular fibroblast cells in the renal cortex in response to tissue hypoxia (as seen with anemia). Healthy individuals increase EPO production up to 10,000-fold in response to anemia, but patients with CKD have chronic renal inflammation that **damages EPO-producing cells**, thereby preventing an adequate EPO response. Therefore, patients with CKD are often treated with **recombinant EPO agents** (eg, epoetin, darbepoetin) to supplement EPO production.

EPO travels from the kidney through the bloodstream to the bone marrow, where it binds to a surface receptor on **erythrocyte colony–forming unit cells** (erythrocyte precursors). Binding activates the Janus kinase 2/signal transducers and activators of transcription (**JAK2/STAT**) signaling pathway, which induces the transcription of proteins that inhibit erythrocyte precursor apoptosis and promote survival. Binding also activates signals that increase the differentiation of erythrocyte precursors into mature erythrocytes. Together, these effects increase the production of erythrocytes and improve circulating red blood cell counts.

Activating mutations affecting the *JAK2* gene are associated with polycythemia vera, a chronic myeloproliferative disorder marked by the clonal proliferation of erythrocytes (leading to dramatic elevations in hematocrit).

(Choice A) Cyclic AMP mediates the effects of a variety of hormones including glucagon, antidiuretic hormone (V2 receptor), and corticotropin. However, this pathway is not a primary intermediate in erythrogenesis.

(Choice B) Cleavage of membrane phospholipids by phospholipase A2 leads to the formation of arachidonic acid, which is in turn converted into prostaglandins and leukotrienes that help regulate the inflammatory response. A variety of medications directly or indirectly affect this system, including glucocorticoids, nonsteroidal anti-inflammatory drugs, and leukotriene inhibitors.

(Choice D) Widely used therapeutic hormones that activate a nuclear receptor include thyroid hormone, vitamins A & D, and the steroid hormones (eg, glucocorticoids, mineralocorticoids, sex hormones).

(Choice E) Therapeutic hormones that activate a phosphatidylinositol second messenger system include antidiuretic hormone (V1 receptor), gonadotropin-releasing hormone, and oxytocin.

(Choice F) The Ras/mitogen-activated protein kinase signal transduction system is used by a variety of growth factors (eg, epidermal growth factor, platelet-derived growth factor), which primarily act to stimulate cell proliferation. Uncontrolled activation of this system can lead to malignancy.

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Educational objective:
Chronic kidney disease is commonly associated with normocytic anemia due to reduced production of erythropoietin by the kidneys. Erythropoietin signal transduction is primarily mediated by the Janus kinase 2/signal transducers and activators of transcription (JAK2/STAT) pathway, which promotes erythrocyte precursor survival.

References

- Urology and nephrology update: anemia of chronic kidney disease.

Physiology	Hematology & Oncology	Chronic kidney disease
Subject	System	Topic

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A 3-week-old boy is brought to the emergency department due to lethargy for a day. The patient was breastfeeding well until this morning, when he became increasingly difficult to arouse. He was born full-term to a 35-year-old mother who had a spontaneous vaginal delivery at home. She took prenatal vitamins throughout pregnancy and received routine prenatal care. However, the boy did not receive any vaccinations or medications after birth due to parental preference for a "natural" newborn period. Family history is unremarkable. Head circumference is at the 99th percentile. Weight and length are at the 25th percentile. Physical examination shows a large, bulging anterior fontanel. The eyes appear driven downward and the patient is not able to track upward. No scalp swelling is present. Intracranial hemorrhage is confirmed on head CT scan. Which of the following is the most likely cause of this infant's condition?

A. Abusive head trauma

B. Bacterial meningitis

C. Birth injury

D. Germinal matrix fragility

E. Impaired clotting factor carboxylation

Submit

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- A. Abusive head trauma (5%)
- B. Bacterial meningitis (19%)
- C. Birth injury (4%)
- D. Germinal matrix fragility (12%)
- ✓ E. Impaired clotting factor carboxylation (58%)

Omitted
Correct answer
E

58%
Answered correctly

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Time Spent

05/04/2020
Last Updated

Explanation

Neonatal vitamin K deficiency	
Etiology	• Low vitamin K stores (poor placental transfer, sterile gut, low content in breast milk)

Neonatal vitamin K deficiency	
Etiology	• Low vitamin K stores (poor placental transfer, sterile gut, low content in breast milk) • Inefficient vitamin K utilization by immature liver
Presentation	• Intracranial, gastrointestinal, cutaneous, umbilical & surgical site bleeding
Prevention	• Intramuscular vitamin K at birth

Vitamin K is an essential cofactor for gamma-glutamyl carboxylase, the enzyme responsible for converting glutamyl residues to gamma-carboxyglutamates. Carboxylation is critical for the function of clotting factors II (prothrombin), VII, IX, and X as it allows for the creation of calcium-binding sites. These sites attract the clotting factors to negatively charged phospholipids on platelets and endothelial cells, encouraging coagulation and thrombin formation.

Healthy children and adults rarely need exogenous vitamin K supplementation as endogenous colonic bacterial flora generates vitamin K and leafy-green vegetables are rich in vitamin K. In contrast, **newborns** have **low vitamin K stores** due to poor transplacental transfer and low content in breast milk. Insufficient levels remain in the first month of life due to delayed production by the gradual colonization of bacterial gut flora as well as insufficient utilization by an immature liver. Neonatal vitamin K deficiency is prevented by administration of intramuscular vitamin K at birth.

Without exogenous vitamin K, as in this patient, vitamin K deficiency results in **impaired clotting factor carboxylation** and, therefore, a propensity for bleeding. **Intracranial hemorrhage** (ICH) is a potentially fatal complication, often presenting with signs of increased intracranial pressure (eg, altered mental status, enlarging head circumference, bulging fontanel, downward-driven eyes).

(Choice A) Abusive head trauma can lead to intracranial bleeding and subdural hemorrhage in infants. This is less likely in an infant with no external trauma signs and no prior vitamin K prophylaxis. If the infant had received a vitamin K injection at birth, abusive head trauma would be the most likely diagnosis.

(Choice B) Neonatal bacterial meningitis can present with lethargy or irritability, but affected patients also have fever or hypothermia. In addition, bacterial meningitis does not typically cause ICH.

(Choice C) ICH from birth injuries is most common in operative deliveries involving vacuum or forceps assistance. Infants with birth injuries are

birth.

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(Choice C) ICH from birth injuries is most common in operative deliveries involving vacuum or forceps assistance. Infants with birth injuries are typically symptomatic shortly after birth rather than at age 1 month.

(Choice D) Germinal matrix fragility is responsible for intraventricular hemorrhage in premature infants. The germinal matrix starts involuting around 28 weeks gestation and disappears by full term.

Educational objective:
Vitamin K deficiency results in impaired clotting factor carboxylation. Newborns are at risk for vitamin K deficiency due to poor transplacental transfer of vitamin K and low content in breast milk. All newborns should receive vitamin K prophylaxis to prevent bleeding complications.

References

- Rise in late onset vitamin K deficiency bleeding in young infants because of omission or refusal of prophylaxis at birth.
- Vitamin K deficiency bleeding: a case study.

Physiology	Hematology & Oncology	Vitamin k deficiency
Subject	System	Topic

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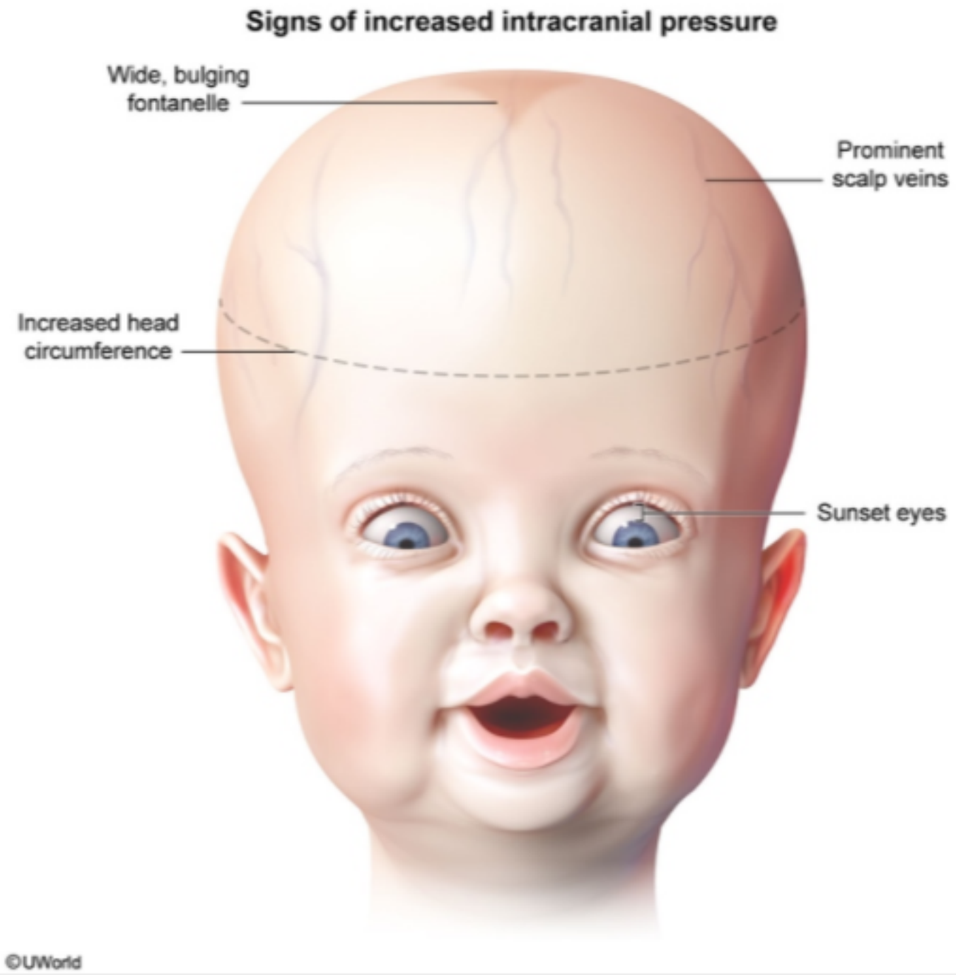
birth.

Exhibit Display



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A 41-year-old woman with a long history of menorrhagia comes to the physician due to a low hemoglobin level identified on routine laboratory evaluation. She is diagnosed with iron deficiency anemia and started on oral ferrous sulfate. After 3 months of therapy, her laboratory values have improved. She now asks about stopping her supplement as she is concerned about iron buildup and damage to vital organs. The physician reassures her and explains that iron homeostasis is maintained by multiple types of cells in the body. Which of the following cells secrete a substance that controls iron storage and release by other cells involved in iron homeostasis?

A. Biliary lining cells

B. Bone marrow macrophages

C. Bone marrow stem cells

D. Hepatic parenchymal cells

E. Intestinal epithelial cells

F. Renal tubular cells

Submit

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- A. Biliary lining cells (0%)
- B. Bone marrow macrophages (11%)
- C. Bone marrow stem cells (1%)
- ✓ D. Hepatic parenchymal cells (66%)
- E. Intestinal epithelial cells (17%)
- F. Renal tubular cells (2%)

Omitted
Correct answer
D

66%
Answered correctly

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Time Spent

04/07/2020
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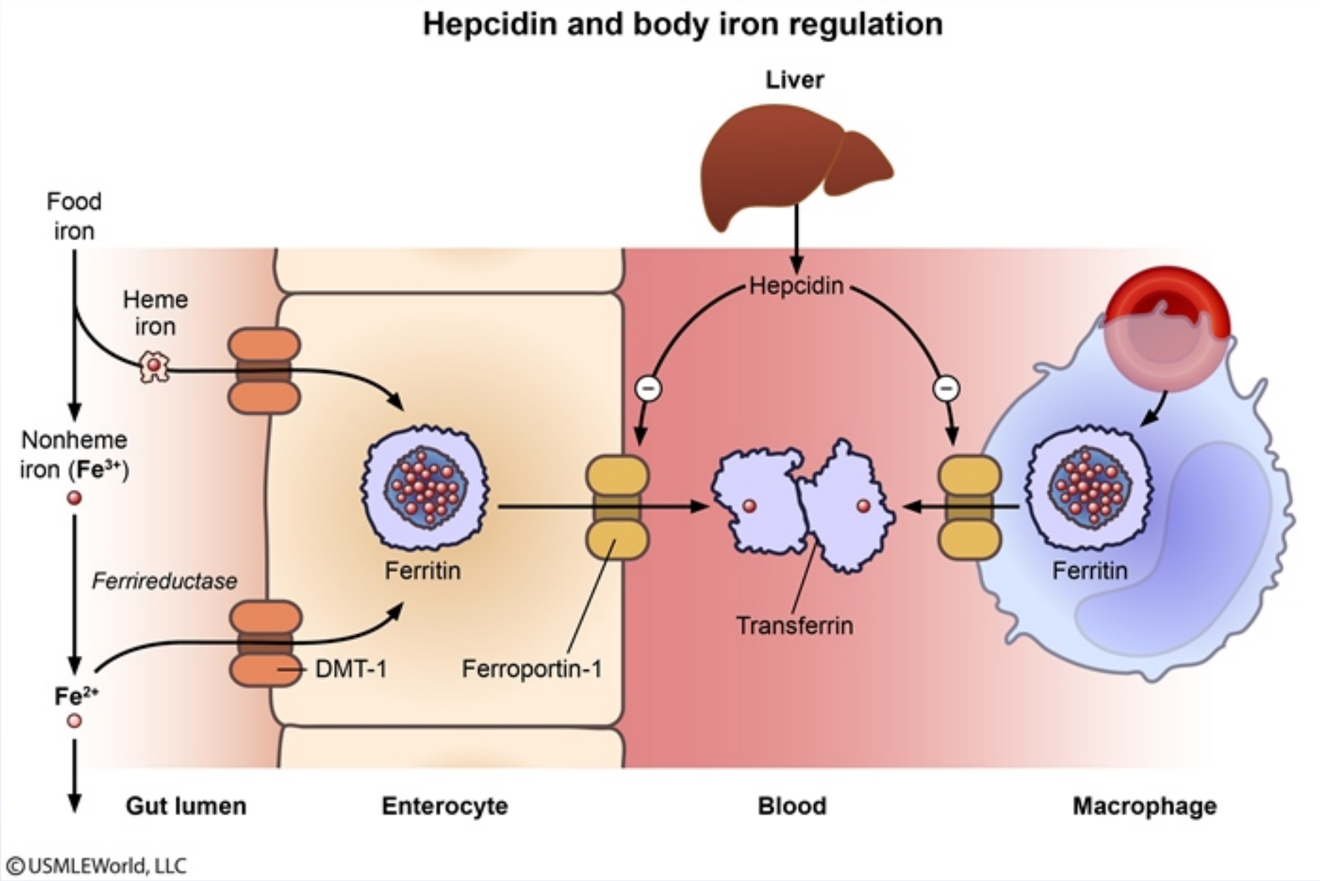
Explanation

Hepcidin and body iron regulation

Liver



Hepcidin is an acute phase reactant synthesized by the liver that acts as the **central regulator of iron homeostasis**. High iron levels and inflammatory conditions increase the synthesis of hepcidin, while hypoxia and increased erythropoiesis act to lower hepcidin levels. Hepcidin influences body iron storage through its interaction with **ferroportin**, a transmembrane protein responsible for transferring intracellular iron to the circulation. Upon binding hepcidin, ferroportin is internalized and degraded, decreasing intestinal iron absorption and inhibiting the release of iron by macrophages.

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Regulation of intestinal iron absorption is crucial for maintaining iron homeostasis, since blood loss is the only way of removing large amounts of iron from the body. Iron absorption from the proximal small intestine is facilitated by the divalent metal transporter-1 (DMT-1). Once inside the intestinal cells, iron may take 1 of 2 paths:

1. Iron may bind to ferritin (a primarily intracellular iron-binding protein) and remain stored within the enterocyte. The stored iron is excreted in the stool as enterocytes slough off and are replaced.
2. Iron may enter the circulation through ferroportin, the basolateral iron transporter of the enterocyte. Free iron released into the circulation is transported throughout the body by transferrin (an iron-binding transport protein), which becomes internalized after interacting with transferrin receptors present on all cells.

(Choice A) Hepcidin is secreted primarily by hepatocytes; biliary cells produce only a limited amount of hepcidin that is mainly excreted in the bile.

(Choices B and C) When senescent red blood cells are destroyed by macrophages, the iron is recycled by the reticuloendothelial system for use in new erythroid precursors. Iron released by macrophages under the governance of hepcidin binds rapidly to transferrin and is delivered to the bone marrow, where erythroid precursors use it to synthesize hemoglobin. This internal iron cycle conserves the body's iron very efficiently, and only small amounts of additional iron are required for daily red cell production in the absence of significant blood loss.

(Choice E) Enterocytes store iron for excretion in the feces or transport it into the circulation depending on circulating levels of the polypeptide hormone hepcidin. Lower hepcidin levels favor iron absorption and accumulation in the body.

(Choice F) The renal tubular cells play a limited role in iron metabolism by secreting lactoferrin, which binds to free iron in the urine and possibly recovers it for metabolic use.

Educational objective:
Hepcidin is a polypeptide synthesized by the liver that acts as the central regulator of iron homeostasis. High iron levels and inflammatory

the stool as enterocytes slough off and are replaced.

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Educational objective:
Hepcidin is a polypeptide synthesized by the liver that acts as the central regulator of iron homeostasis. High iron levels and inflammatory conditions increase the synthesis of hepcidin; hypoxia and increased erythropoiesis act to lower hepcidin levels. Low hepcidin levels increase intestinal iron absorption and stimulate iron release by macrophages.

References

- Regulation of cellular iron metabolism

Physiology	Hematology & Oncology	Iron deficiency anemia
Subject	System	Topic

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A 70-year-old man comes to the office due to palpitations. He has felt an irregular and fast heartbeat on multiple occasions over the last month. The patient has not had chest pain, dyspnea, dizziness, or weakness. His medical history includes hypertension and type 2 diabetes mellitus. Temperature is 36.7 C (98.1 F), pulse is 102/min and irregular, blood pressure is 140/82 mm Hg, and respirations are 16/min. Cardiopulmonary auscultation reveals clear lungs and no heart murmurs. ECG shows an irregularly irregular rhythm with absent P waves. The patient is started on metoprolol and apixaban. Which of the following is likely to be directly affected as the result of this therapy?

A. Conversion of factor X to Xa

B. Conversion of fibrinogen to fibrin

C. Conversion of plasminogen to plasmin

D. Conversion of prothrombin to thrombin

E. Gamma-carboxylation of coagulation factors

Submit

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A. Conversion of factor X to Xa (58%)

B. Conversion of fibrinogen to fibrin (4%)

C. Conversion of plasminogen to plasmin (1%)

✓ D. Conversion of prothrombin to thrombin (33%)

E. Gamma-carboxylation of coagulation factors (0%)

Omitted
Correct answer
D

33%
Answered correctly

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02/16/2020
Last Updated

Explanation

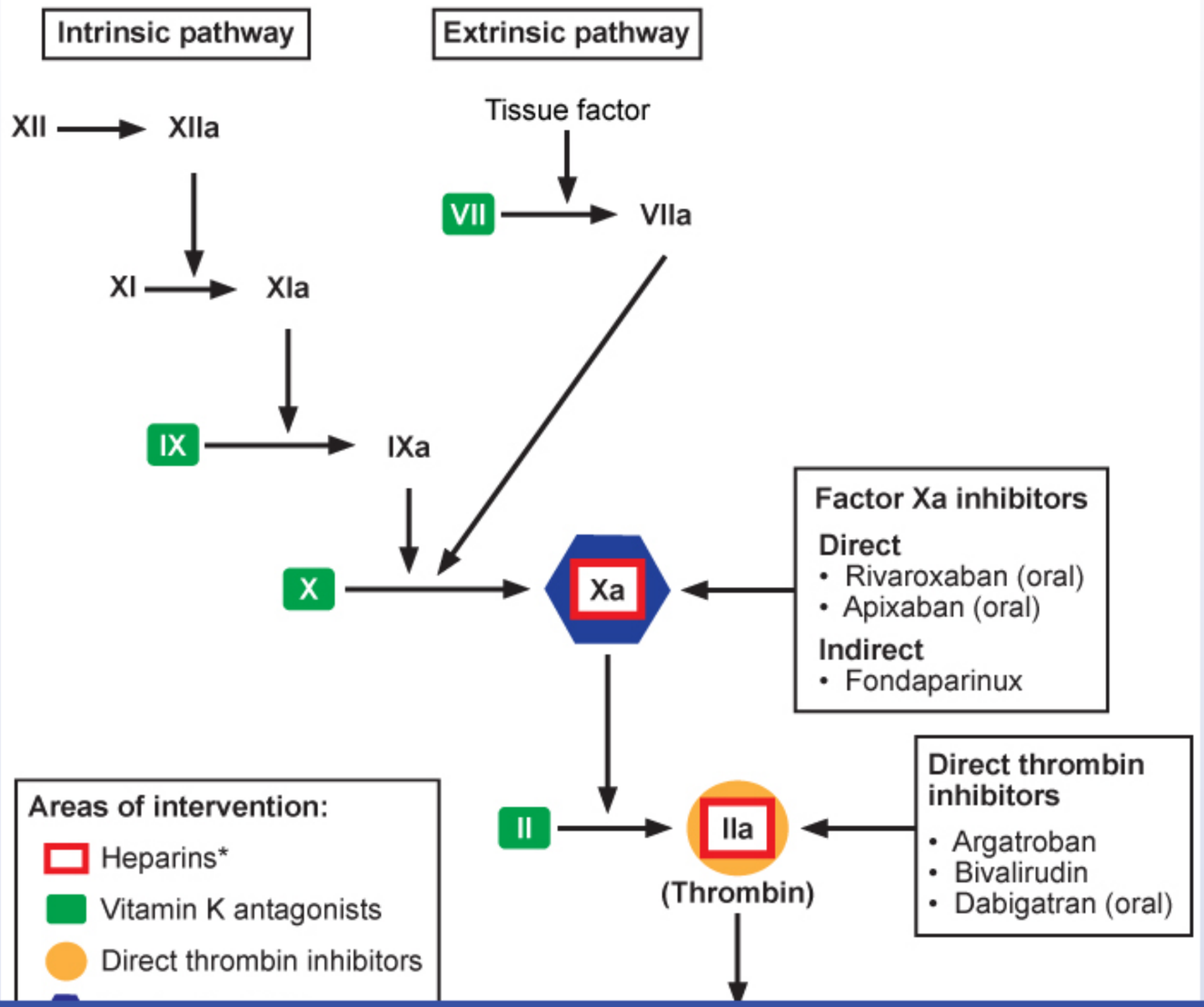
Anticoagulants & their mechanism of action

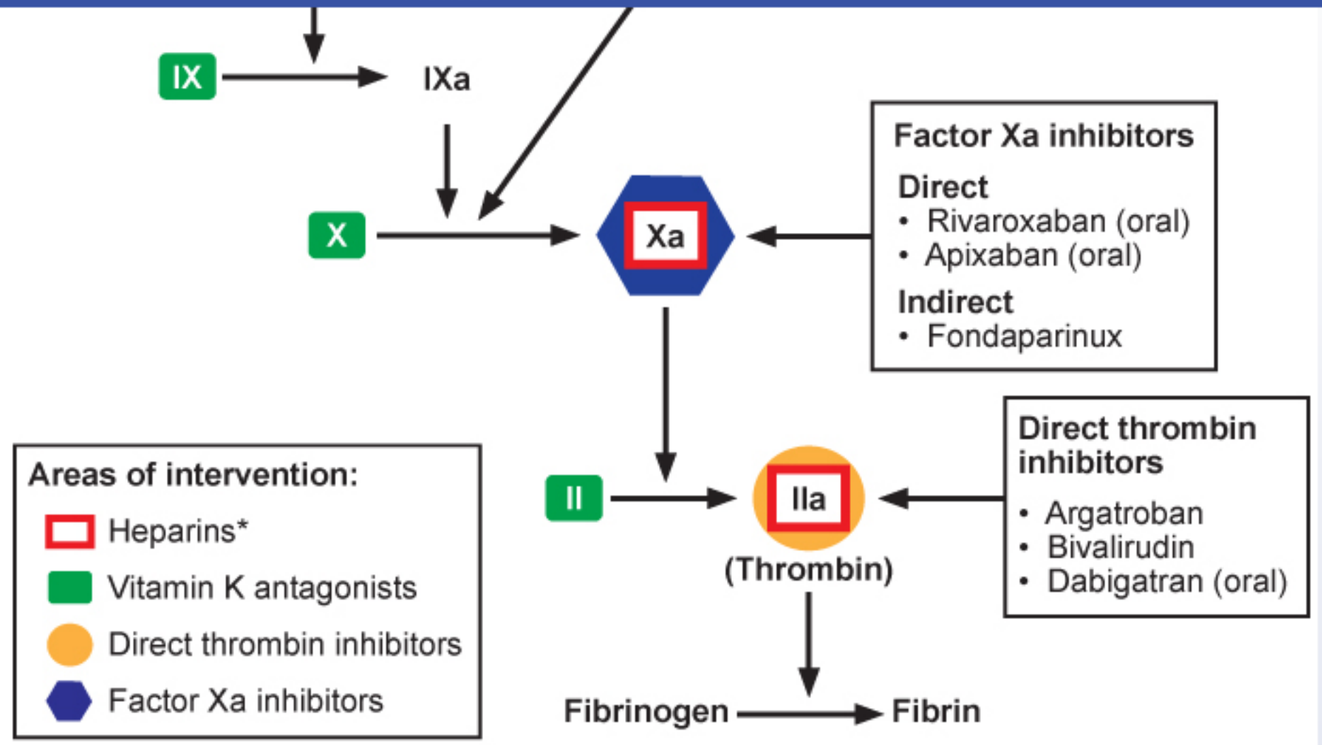
Intrinsic pathway

Extrinsic pathway

Tissue factor

Anticoagulants & their mechanism of action





*Major mechanism of action; antithrombin III has some inhibition on all activated coagulation factors.
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This patient has palpitations, an irregular pulse, and ECG findings consistent with **atrial fibrillation**. Treatment with a rate control medication (eg, metoprolol) reduces atrioventricular conduction and limits ventricular tachycardia, which helps prevent symptoms (eg, palpitations, dizziness) and risk of cardiomyopathy. However, rate control agents do not inhibit uncoordinated atrial contraction, so patients remain at risk for atrial thrombus and embolic stroke. As a result, most patients are also initiated on **anticoagulation**.

Direct factor Xa inhibitors (eg, apixaban) are often used for stroke prevention in atrial fibrillation as they are administered orally and do not require monitoring of drug levels (unlike warfarin). This class of medications blocks the active site of factor Xa, which prevents it from converting **prothrombin to thrombin**. Direct factor Xa inhibitors are denoted by names that end in "**Xa**-ban."

(Choice A) The conversion of factor X to factor Xa is the beginning the final common pathway of the coagulation cascade and is triggered by

This patient has palpitations, an irregular pulse, and ECG findings consistent with **atrial fibrillation**. Treatment with a rate control medication (eg, metoprolol) reduces atrioventricular conduction and limits ventricular tachycardia, which helps prevent symptoms (eg, palpitations, dizziness) and risk of cardiomyopathy. However, rate control agents do not inhibit uncoordinated atrial contraction, so patients remain at risk for atrial thrombus and embolic stroke. As a result, most patients are also initiated on **anticoagulation**.

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(Choice A) The conversion of factor X to factor Xa is the beginning the final common pathway of the coagulation cascade and is triggered by factor VIIIa (intrinsic pathway) and tissue factor (extrinsic pathway). Factor Xa inhibitors block conversion of prothrombin to thrombin, not factor X to factor Xa.

(Choice B) Factor Xa inhibitors reduce the conversion of fibrinogen to fibrin. However, this is a downstream (not direct) effect that occurs as a result of decreased thrombin levels.

(Choice C) Tissue plasminogen activator is a fibrinolytic enzyme that increases the conversion of plasminogen to plasmin. It is primarily used to lyse ongoing clots in patients with acute ischemic strokes.

(Choice E) Warfarin inhibits vitamin K epoxide reductase, which decreases the reduced form of vitamin K and limits gamma-carboxylation of vitamin K–dependent coagulation factors (II, VII, IX, X).

Educational objective:
Direct factor Xa inhibitors (eg, apixaban) are anticoagulants that block the active site of factor Xa, which leads to reduced conversion of prothrombin to thrombin. This class of medications is administered orally and requires no drug level monitoring.

Physiology	Hematology & Oncology	Atrial fibrillation
Subject	System	Topic

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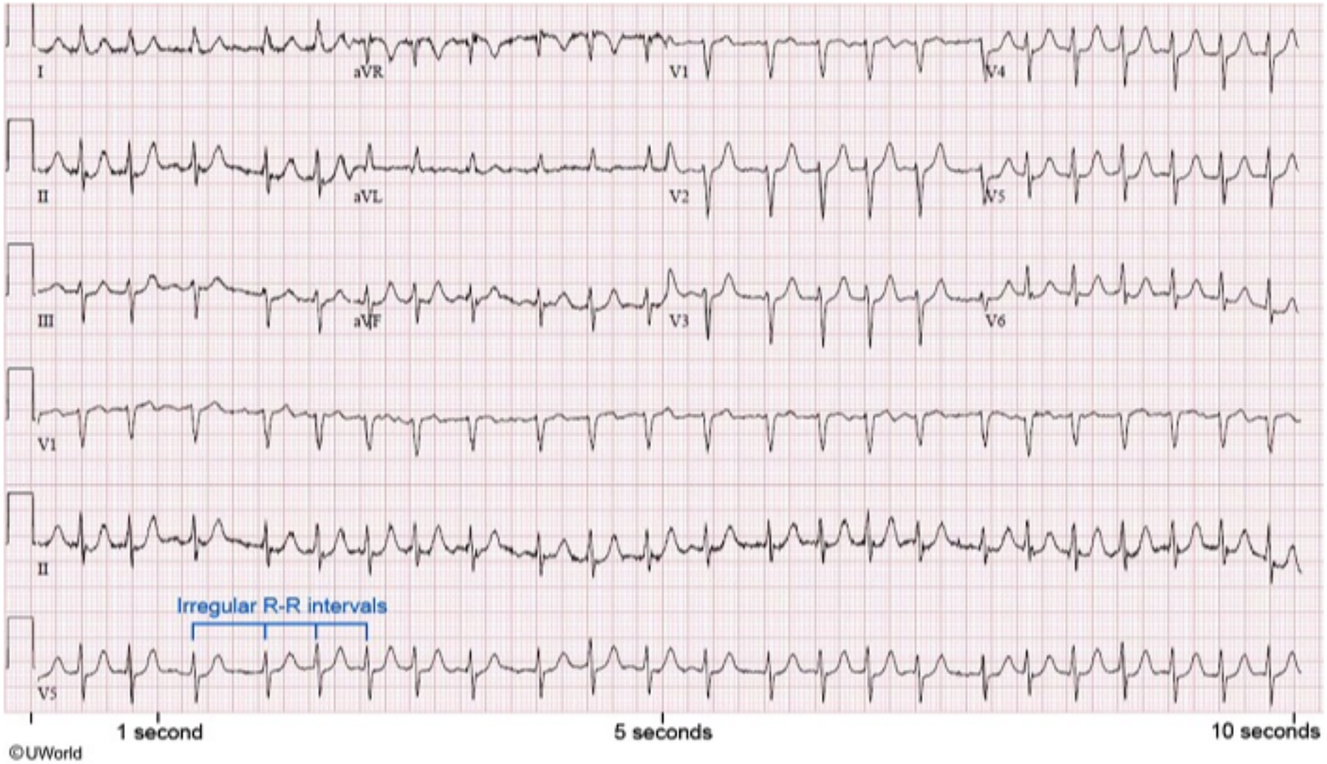

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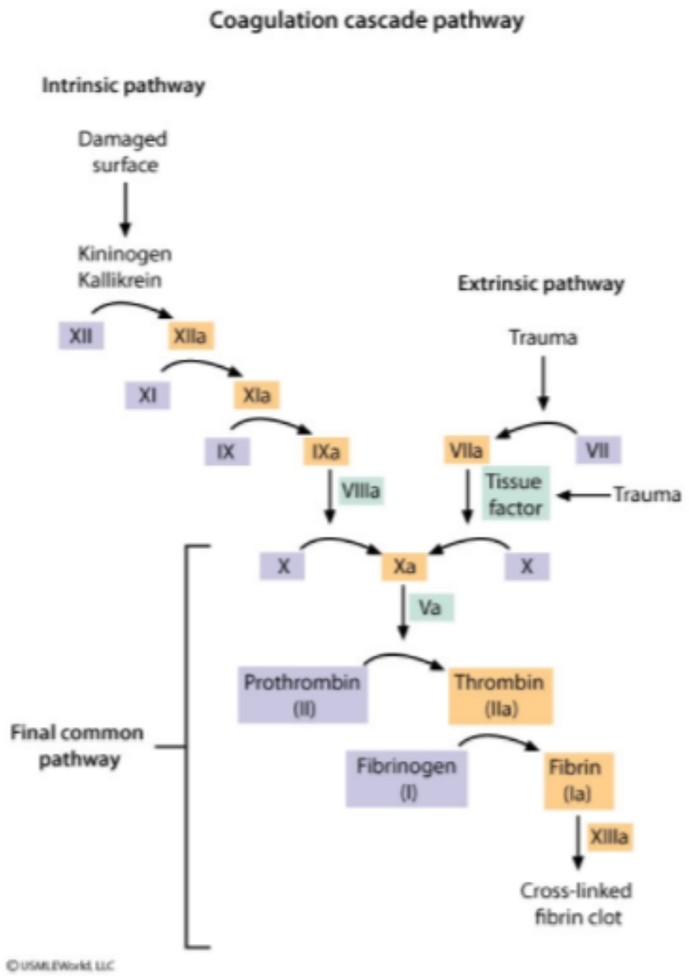

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A 6-year-old girl is brought to the office by her mother due to abdominal pain and vomiting. The patient has Down syndrome but has otherwise been healthy. Abdominal examination reveals the liver edge 3 cm below the costal margin and the spleen tip extending past the level of the umbilicus. Leukocyte count is 104,000/mm^3, and subsequent peripheral blood smear reveals numerous lymphoblasts. The patient is diagnosed with acute lymphoblastic leukemia and combination cytotoxic chemotherapy is planned. Which of the following laboratory changes are most likely to be seen in this patient following treatment initiation?

	Potassium	Uric acid	Phosphorous	Lactate dehydrogenase
A.	↓	↑	↑	↑
B.	↓	↑	↓	↑
C.	↑	↓	↓	↑
D.	↑	↑	↓	↓
E.	↑	↑	↑	↓
F.	↑	↑	↑	↑

Submit

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	Potassium	Uric acid	Phosphorous	Lactate dehydrogenase
A. (10%)	↓	↑	↑	↑
B. (7%)	↓	↑	↓	↑
C. (2%)	↑	↓	↓	↑
D. (4%)	↑	↑	↓	↓
E. (5%)	↑	↑	↑	↓
✓ F. (69%)	↑	↑	↑	↑

Omitted
Correct answer
F

69%
Answered correctly

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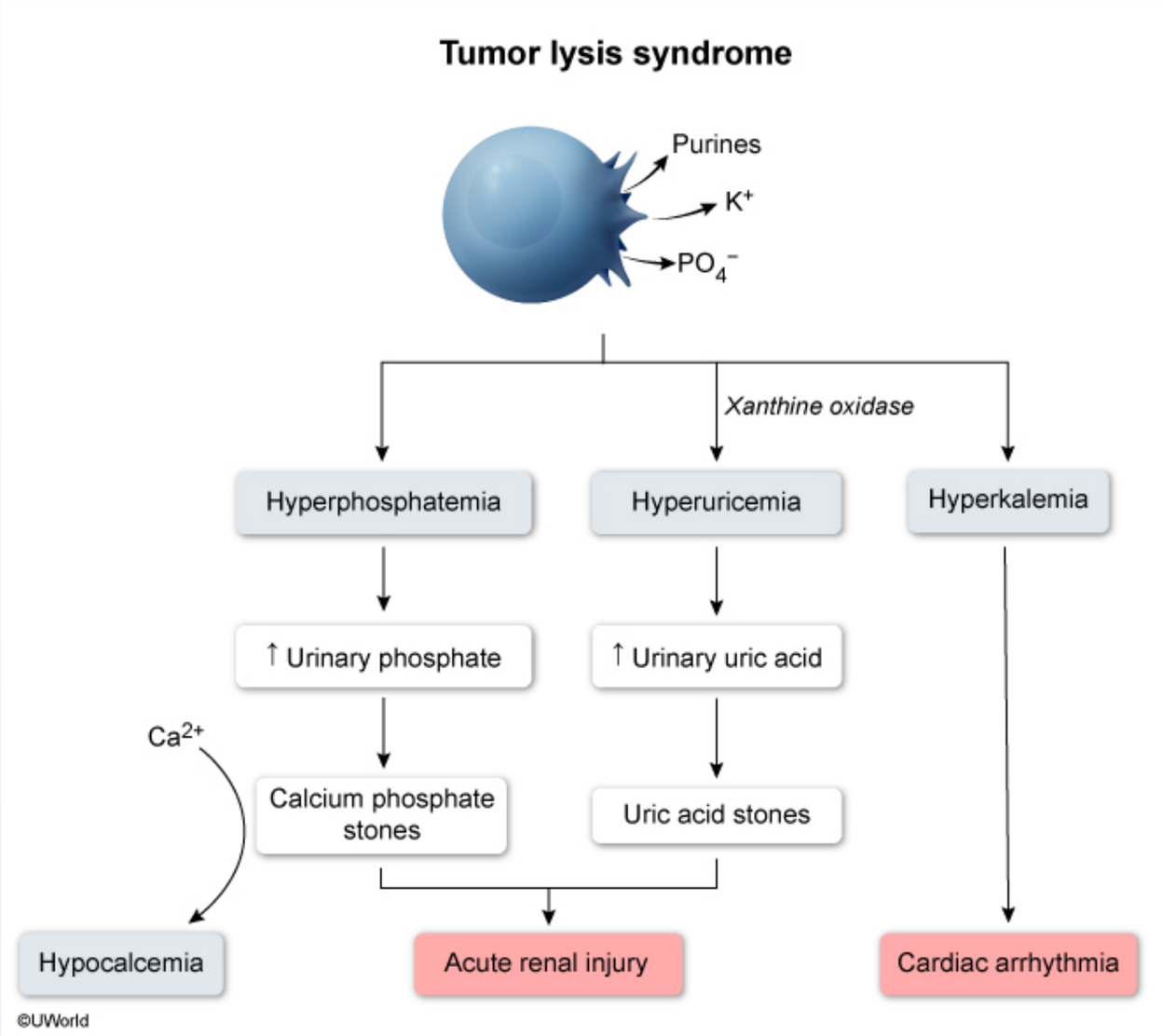

Acute lymphoblastic leukemia (ALL) is a hematologic malignancy that is generally associated with a high tumor cell burden and a rapid turnover

Hypocalcemia | Acute renal injury | Cardiac arrhythmia

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Acute lymphoblastic leukemia (ALL) is a hematologic malignancy that is generally associated with a high tumor cell burden and a rapid turnover rate. Therefore, initiation of cytotoxic chemotherapy often leads to massive lysis of tumor cells, which spills intracellular contents into the blood (**tumor lysis syndrome**), resulting in the following:

- **Hyperphosphatemia:** Intracellular phosphate concentration is much higher than serum phosphate levels. Therefore, serum phosphate levels typically spike following chemotherapy initiation. Because excess phosphate is excreted via the kidneys, patients are at risk for calcium-phosphate deposition in the renal tubules and collecting system, which can lead to hypocalcemia and acute renal failure.
- **Hyperuricemia:** Purine nucleic acids released from lysed tumor cells are metabolized by xanthine oxidase into uric acid. Because uric acid is excreted through the kidneys and is poorly soluble, patients are at risk for obstructing uric acid stones, which can lead to acute renal injury.
- **Hyperkalemia:** Potassium is primarily an intracellular ion. Therefore, significant tumor lysis is generally associated with elevations of serum potassium, which can lead to cardiac arrhythmia.
- **Elevated lactate dehydrogenase** (LDH): Lactate dehydrogenase, an enzyme involved in cellular respiration, is found in almost all human cells. It is an important laboratory marker for cell lysis in a wide range of disease states (eg, hemolytic anemia). Levels are typically significantly elevated in tumor lysis syndrome.

Educational objective:
Patients with hematologic malignancies that have high tumor cell burdens or rapid turnover rates are at high risk for electrolyte abnormalities following the initiation of cytotoxic chemotherapy due to the massive lysis of tumor cells. Patients generally develop hyperphosphatemia, hyperkalemia, hyperuricemia, and elevated lactate dehydrogenase.

Physiology	Hematology & Oncology	Tumor lysis syndrome
Subject	System	Topic

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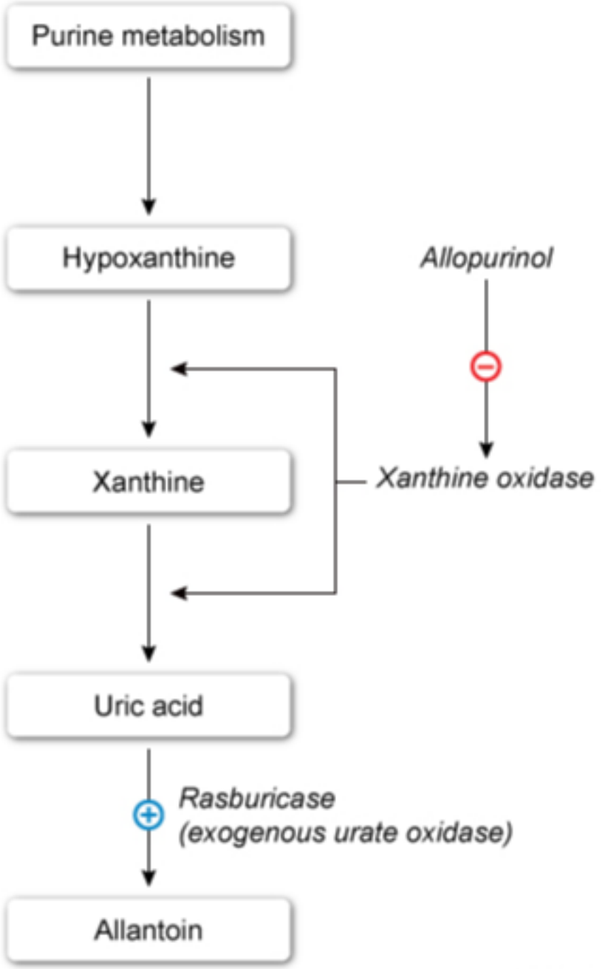

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